UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/715,876	11/18/2000	John E. Edwards JR.	259/064	7636

34313 7590 09/15/2004

ORRICK, HERRINGTON & SUTCLIFFE, LLP
4 PARK PLAZA
SUITE 1600
IRVINE, CA 92614-2558

EXAMINER	
DEVI, SARVAMANGALA J N	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 09/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/715,876	EDWARDS ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 June 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3 and 9-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3 and 9-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE O APPLICANTS' AMENDMENT

Applicants' Amendment

1) Acknowledgment is made of Applicants' amendment filed 06/21/04 in response to the non-final Office Action mailed 02/18/04. With this, Applicants have amended the specification.

Status of Claims

2) Claims 1 and 9 have been amended via the amendment filed 06/21/04.

New claims 10-12 have been added via the amendment filed 06/21/04.

Claims 1, 3 and 9-12 are pending and are under examination.

Prior Citation of Title 35 Sections

3) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

4) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Objection(s) Maintained

5) The objection to the drawing made in paragraph 5 of the Office Action mailed 04/09/03 and maintained in paragraph 7 of the Office Action mailed 02/18/04 is maintained for reasons set forth therein. Applicants have assured the Office that they would submit the required formal drawings upon the receipt of the Notice of Allowability.

Objection(s) Withdrawn

6) The objection to the specification made in paragraph 8 of the Office Action mailed 02/18/04 is withdrawn in light of Applicants' amendment to the specification.

Rejection(s) Withdrawn

7) The rejection of claim 1 made in paragraph 18(a) of the Office Action mailed 02/18/04 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

8) The rejection of claims 3 and 9 made in paragraph 18(c) of the Office Action mailed 02/18/04 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of

Applicants' amendment to the base claim.

9) The rejection of claims 1, 3 and 9 made in paragraph 20 of the Office Action mailed 02/18/04 under 35 U.S.C § 103(a) as being unpatentable over Hoyer *et al.* (*Mol. Microbiol.* 15: 39-54, 1995, already of record) (Hoyer *et al.*, 1995) in view of Applicants' admitted state of the prior art, is withdrawn in light of Applicants' amendment particularly to claim 9.

Rejection(s) Maintained

10) The rejection of claim 9 made in paragraph 18(b) of the Office Action mailed 02/18/04 under 35 U.S.C § 112, second paragraph, as being indefinite, is maintained for reasons set forth therein.

11) The rejection of claims 1 and 3 made in paragraph 19 of the Office Action mailed 02/18/04 under 35 U.S.C § 102(b) as being anticipated by Hoyer *et al.* (*J. Bacteriol.* 180: 5334-5343, October 1998, already of record), is maintained for reasons set forth therein and herebelow.

Applicants contend that Hoyer *et al.* (1998) described the PCR amplification of a polynucleotide encoding a 433 amino acid N-terminal fragment of ALS1 protein. Applicants acknowledge that the ALS1 N-terminal fragment was dissolved in and dialyzed against PBS, but only as part of a mixture of other peptides. Applicants state that the fragment was solubilized for subsequent use in biochemical characterization experiments, such as electrophoresis. Applicants submit that 'Hoyer *et al.* (1998) did not formulate the 433 amino acid fragment in an isolated and purified composition'. Applicants state that when Hoyer *et al.* (1998) desired to create anti-ALS1 antibodies, they used a mixture of four 10-mer peptides derived from conserved regions of ALS1 as antigen to produce ALS1 antiserum. Applicants assert that this is not the isolated and purified compound of the claims. Applicants contend that they have formulated the isolated and purified N-terminal fragment of ALS1 protein together with a biocompatible carrier and used this composition to elicit an *in vivo* immune response, and demonstrated that ALS1-antiserum obtained to the N-terminal region of ALS1 protein blocked the adherence of ALS1 to endothelial cells. Applicants state that Hoyer *et al.* (1998): (a) did not use the purified 433 amino acid protein as an antigen to produce anti-Als antiserum; (b) did not teach the use of the protein fragment as antigen; and (c) did not disclose the usefulness of ALS1 antiserum to block adherence of ALS1 to endothelial cells. Applicants assert that on the contrary Applicants show data for the binding of ALS1 to endothelial

cells; the identification of ALS1 as a downstream effector of filamentation and ensuing virulence; and the blocking of binding with ALS1-antiserum. Applicants state that Hoyer *et al.* (1998) disclosed the use of an anti-Als antiserum to test variation in length of Als proteins.

Applicants' arguments have been carefully considered, but are non-persuasive. Applicants should note that the instant claims are not directed to: (a) a method of use of ALS1 antiserum to block adherence of ALS1 to endothelial cells; or (b) a method of identification of ALS1 as a downstream effector of filamentation and ensuing virulence. On the contrary, instant claims are directed to a pharmaceutical composition. Applicants' acknowledgment that Hoyer *et al.* (1998) taught a 433 amino acid-long N-terminal fragment of ALS1 protein of *Candida albicans* dissolved in PBS has been noted. More importantly, Applicants' admission that Hoyer *et al.* (1998) used a mixture of four 10-mer peptides derived from conserved regions of ALS1 as antigen to produce anti-ALS1 antiserum has been noted.

As previously explained to Applicants, instant claims 1 and 3, as amended currently, do not define the claimed N-terminal fragment by its structure or amino acid composition, i.e., SEQ ID number. The claimed N-terminal protein fragment does not exclude Hoyer's (1998) N-terminal protein fragment. Since the N-terminal fragment of claims 1 and 3 is not identified by one or more structural limitations, it includes or encompasses Hoyer's (1998) or any other isolated and purified N-terminal fragment protein of *Candida albicans*. Hoyer *et al.* (1998) do teach the claimed composition comprising a biocompatible carrier (see below). The functional limitation, i.e., production of an effective immune response, on which the prior art reference is allegedly silent, is considered as an inherent property inseparable from the prior art N-terminal protein fragment. Where the only difference between the claimed product and the prior art product is recited in the functional language, i.e., by what it does rather than what it is, it is incumbent upon Applicants, when challenged by the USPTO, to demonstrate that the prior art product does not actually possess those characteristics. Applicants have not established that Hoyer's (1998) isolated and purified 433 amino acid-long 65-kDa N terminal fragment contained in PBS is incapable of producing an effective immune response n a patient. With regard to Applicants' remarks on Hoyer's (1998) use of a mixture of four 10-mer peptides derived from ALS1 to produce ALS1 antiserum, it should be noted that this part of Hoyer's (1998) disclosure was not cited by or referred to in the Office's

rejection. *Arguendo*, even if it was cited or referred to, Hoyer's (1998) disclosure of a mixture of four 10-mer peptides from the 'N-terminal domain of Als1p', GWSLDGTSAN (amino acids 53 to 62); FYSGEEFTTF (amino acids 98 to 107); TGSSTDLEDS (amino acids 139 to 148); and NTVTFNDGDK (amino acids 156 to 165), conjugated to KLH, contained in an adjuvant and eliciting anti-ALS1 antibodies, as taught in the fifth full paragraph in the right column of page 5335 of Hoyer *et al.* (1998), would clearly anticipate the claimed composition. This is because the open-ended transitional claim language in claim 1 'comprising' does not exclude additional, unrecited N-terminal fragment elements. The transitional term "comprising" or "containing" is synonymous with "including," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. *Moleculon Research Corp. v. CBS, Inc.*, 793 F.2d 1261, 229 USPQ 805 (*Fed. Cir.* 1986); *In re Baxter*, 656 F.2d 679, 686, 210 USPQ 795, 803 (*CCPA* 1981); *Ex parte Davis*, 80 USPQ 448, 450 (*Bd. App.* 1948) ("comprising" leaves "the claim open for the inclusion of unspecified ingredients even in major amounts"). See MPEP 2111.03 [R-1]. Hoyer's (1998) teaching of 'N-terminal domain of Als1p' fragments, GWSLDGTSAN (amino acids 53 to 62); FYSGEEFTTF (amino acids 98 to 107); TGSSTDLEDS (amino acids 139 to 148); and NTVTFNDGDK (amino acids 156 to 165), in fact fully supports the anticipatory basis of the Office's rejection. In view of Hoyer's (1998) showing that a peptide as short as a 10-mer N-terminal fragment of Als1p produces an effective immune response, an Als1p N-terminal fragment as lengthy as 433 amino acids-long is expected by those of skill in the art to produce an effective immune response in a patient, even without conjugation to a carrier protein and/or without being administered in an adjuvant. As set forth previously, it is well known in the art that a microbial protein fragment as long as the one taught by Hoyer *et al.* is long enough to serve intrinsically as an effective immunogen, being capable of producing an effective immune response in a patient, absent evidence to the contrary. As set forth below, the instantly claimed composition is anticipated by Hoyer *et al.* (1998).

Hoyer's (1998) taught a composition, which comprises the isolated and purified N-terminal domain of an adhesion protein, Als1p, of *Candida albicans* dissolved in PBS, i.e., a biocompatible carrier for injection or infusion (see pages 5334, 5336 and 5337). Hoyer *et al.* (1998) taught the 65-kDa N-terminal fragment and the amino acid sequencing of this Als1p-derived 'fragment' in the

third full paragraph of the left column of page 5336. Hoyer *et al.* (1998) taught therein that the 65-kDa band from culture supernatant was gel separated (i.e., purified) from the sparse number of the protein band. The protein from the gel was electroblotted on to a membrane, which was rinsed thoroughly with deionized water. The Als1p-derived fragment was excised and the N-terminal amino acid sequencing was performed. Noteworthy is that in the second full paragraph in the left column of page 5336, Hoyer *et al.* (1998) taught the heterologous expression of 'an N-terminal fragment of *Candida albicans* Als1p in *Saccharomyces cerevisiae*. Thus, Hoyer *et al.* (1998) taught the recombinant expression of the N-terminal fragment of *Candida albicans* Als1p in a heterologous host. The recombinant N-terminal portion of Als1p secreted into the culture supernatant was ammonium sulfate-precipitated, centrifuged, the precipitate collected, dissolved in PBS (i.e., a biocompatible carrier), and thoroughly dialyzed against PBS in a dialysis tubing having a molecular weight cut off of 12,000 to 14,000. The dialysate was concentrated. The resultant product comprising the N-terminal portion of Als1p meets the claimed product in that: (a) the N-terminal portion of Als1p is isolated from the cellular mass of the microorganism; and (b) the N-terminal portion of Als1p is purified in that it is free of other antigens of *Candida albicans* since it is recombinantly expressed in a heterologous host such as *Saccharomyces cerevisiae*. Due to the multiple purification steps, such as, ammonium sulfate precipitation, centrifugal separation and dialysis followed by concentration, Hoyer's N-terminal fragment is sufficiently purified for inclusion in a pharmaceutical composition. The purified, dialyzed and concentrated final prior art N-terminal fragment product contained in PBS qualifies as a pharmaceutical composition comprising a biocompatible carrier. The recitation 'for injection or infusion' in claim 10 represents the intended use of the product and has no patentable weight. It is important to note that Hoyer's (1998) N-terminal fragments, GWSLDGTSAN (amino acids 53 to 62); FYSGEEFTTF (amino acids 98 to 107); TGSSTDLEDS (amino acids 139 to 148); and NTVTFNDGDK are the same fragments present in the N-terminal portion of the *Candida albicans* ALS1 protein taught by Hoyer *et al.* (1995). See the sequence alignment report provided along with the Office Action mailed 02/18/04. The rejection stands.

New Rejection(s)

Applicants are asked to note the following new rejection(s) made in this Office. The new

rejections are necessitated by Applicants' amendments to the claim(s) and submission of new claims.

Rejection(s) under 35 U.S.C. § 112, First Paragraph (New Matter)

12) Claims 9 and 12 are rejected under 35 U.S.C § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 9 and 12 include the limitation: 'the ALS1 protein' is encoded by nucleotides 52 to 1296 of SEQ ID NO: 7. However, there appears to be no descriptive support in the specification, as originally filed, for the limitation. Instead, at lines 14-16 on page 18, the instant specification describes that nucleotides 52 to 1296 represent a 'fragment' of ALS1 which encompasses the N-terminal of the predicted ALS1 protein from the end of the signal peptide. This does not provide descriptive support for the now recited limitation: 'the ALS1 protein is encoded by nucleotides 52 to 1296 of SEQ ID NO: 7'. Therefore, the above-identified limitation in the claims is considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to point to the descriptive support in the specification as filed, for the newly added limitation(s), or to remove the new matter from the claim(s).

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

13) Claims 10-12 are rejected under 35 U.S.C § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claim 10 is incorrect in the recitation: 'agluttinin' as opposed to the limitation --agglutinin--.

(b) Claims 11 and 12, which depend from claim 10, are also rejected as being indefinite because of the vagueness or indefiniteness identified above in the base claim.

Rejection(s) under 35 U.S.C. § 102

14) New claims 10 and 11 have been rejected under 35 U.S.C § 102(b) as being anticipated by Hoyer *et al.* (*J. Bacteriol.* 180: 5334-5343, October 1998, already of record) as evidenced by Harlow *et al.* (*In*: *Antibodies*: *A laboratory Manual.* Cold Spring Harbor Laboratory, Chapter 5, p. 76, 1988).

Hoyer's (1998) taught a composition, which comprises the purified N-terminal domain of an adhesion protein, Als1p, of *Candida albicans* dissolved in PBS, i.e., a biocompatible carrier for injection or infusion (see pages 5334, 5336 and 5337). Hoyer *et al.* (1998) taught the 65-kDa N-terminal fragment and the amino acid sequencing of this Als1p-derived 'fragment' in the third full paragraph of the left column of page 5336. Hoyer *et al.* (1998) taught therein that the 65-kDa band from culture supernatant was gel separated (i.e., purified) from the sparse number of the protein bands. The protein from the gel was electroblotted on to a membrane, which was rinsed thoroughly with deionized water. The Als1p-derived fragment was excised and the N-terminal amino acid sequencing was performed. Noteworthy is that in the second full paragraph in the left column of page 5336, Hoyer *et al.* (1998) taught the heterologous expression of 'an N-terminal fragment of *Candida albicans* Als1p in *Saccharomyces cerevisiae*. Thus, Hoyer *et al.* (1998) taught the recombinantly produced N-terminal fragment of *Candida albicans* Als1p via a heterologous host. The recombinant N-terminal portion of Als1p secreted into the culture supernatant was ammonium sulfate-precipitated, centrifuged, the precipitate collected, dissolved in PBS (i.e., a biocompatible carrier), and thoroughly dialyzed against PBS in a dialysis tubing having a molecular weight cut off of 12,000 to 14,000. The dialysate was concentrated. The resultant product comprising the N-terminal portion of Als1p meets the claimed product in that: (a) the N-terminal portion of Als1p is isolated from the cellular mass of the microorganism; and (b) the N-terminal portion of Als1p is purified in that it is free of other antigens of *Candida albicans* since it is recombinantly expressed in a heterologous host such as *Saccharomyces cerevisiae*. Furthermore, due to the multiple purification steps, such as, ammonium sulfate precipitation, centrifugal separation, and dialysis followed by concentration, Hoyer's isolated N-terminal fragment is sufficiently purified for inclusion in a pharmaceutical composition. The purified, dialyzed and concentrated final prior art N-terminal fragment product contained in PBS qualifies as a pharmaceutical composition consisting

essentially of a biocompatible carrier and an isolated and purified N-terminal fragment of ALS1 obtained from *Candida albicans,* as recited. The recitation 'for injection or infusion' in claim 10 represents the intended use of the product and has no patentable weight. Hoyer's (1998) isolated and purified 433 amino acid-long N-terminal fragment contained in PBS is expected to produce an effective immune response in a patient, because the art recognizes that the smallest peptide which elicits antibodies that bind to the original full length protein is 6 amino acids in length. See first sentence under 'Size of the Peptide' on page 76 of Harlow *et al.*

The teachings of Hoyer *et al.* (1998) anticipate the instant claims. Harlow *et al.* is **not** used as a secondary reference in combination with Harlow *et al.* (1998), but rather is used to show that every element of the claimed subject matter is disclosed by Harlow *et al.* (1998) with the unrecited limitation(s) being inherent in view of what is known in the art as explained above. See *In re Samour* 197 USPQ 1 (CCPA 1978).

Claims 10 and 11 are anticipated by Hoyer *et al.* (1998).

Remarks

15) Claims 1, 3 and 9-12 stand rejected.

It is noted that claim 1 includes a misspelled limitation: 'agluttinin'.

16) Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** Applicants are reminded of the extension of time policy as set forth in 37 C.F.R 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

17) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center, which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The RightFax

number for submission of amendments, responses or papers is (703) 872-9306.

18) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

19) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

September, 2004

S. DEVI, PH.D.
PRIMARY EXAMINER